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Two cases of rattlesnake envenomation with delayed coagulopathy

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To the Editor:

The US Food and Drug Administration recently approved the polyvalent crotaline Fab antivenom (CroFab, Protherics, Inc., Nashville, TN). An important feature of the Fab product is its short duration of action. The clinical significance of this is not known, but the much shorter half-life of the CroFab when compared with the Wyeth-Ayerst equine-derived antivenom (Wyeth-Ayerst Pharmaceuticals, St. Davids, PA) and the pharmacodynamic mismatch between venom and antivenom are thought to be possible causes of delayed or recurrent coagulopathy.[1] We describe 2 cases of rattlesnake envenomations with markedly delayed coagulopathy.

Case 1

A 66-year-old man was envenomated in the hand by a Northern Pacific rattlesnake. He developed swelling to his deltoid during the next 6 hours, despite administration of a total of 12 vials of CroFab. The initial platelet count of 14,000/mm^3 corrected after transfusion of 6 units of platelets and antivenom administration. The results of other coagulation tests were normal. During the subsequent 2 days, he received 10 additional vials of CroFab. Five days after the bite, the fibrinogen was less than 50 mg/dL and the D-dimer was 4,000 to 8,000 ng/mL. He remained stable without evidence of bleeding and was discharged on day 6.

Case 2

A 70-year-old woman was envenomated in the hand by a Northern Pacific rattlesnake, with prompt onset of local and systemic toxicity including swelling to the elbow, wheezing, and perioral numbness. Initial laboratory studies were normal and remained normal until 5 days after the bite. During the first 48 hours, she received a total of 18 vials of CroFab. On day 5, her fibrinogen was less than 50 mg/dL, with normal platelet count and otherwise normal coagulation studies. No additional CroFab was given. On hospital day 6, her fibrinogen was less than 50 mg/dL, her international normalized ratio was 6.7, and her activated partial thromboplastin time was more than 240 seconds. There was still no clinical evidence of bleeding. She received an additional 4 vials of CroFab on hospital day 7, and her coagulation studies corrected, except for a fibrinogen of 94 mg/dL. She was discharged home with follow-up on day 8. Follow-up on day 11 revealed normal coagulation studies.

Recurrent coagulopathy was described in the reports by Boyer and Seifert[2] and Boyer et al.[1,3] We have observed markedly delayed coagulopathy in 2 patients who had a satisfactory initial response to CroFab. It is also remarkable that the patient in case 2 had no apparent coagulopathy until day 5 and represents a true late occurrence of a

coagulopathy. The package insert for CroFab recommends an initial dose of 4 to 6 vials followed by 2 vials every 6 hours for a period of 18 hours.[4] Both of our patients received doses exceeding this schedule. Patients treated using this regimen may experience a recurrence or delayed onset of laboratory evidence of serious coagulopathy. Thus, prolonged observation and close follow-up are recommended. An unanswered question is whether abnormal laboratory values translate into clinical bleeding. It is too early to know whether additional antivenom is needed for such patients, and if so, how much is needed and for how long. The expense of CroFab and patient safety concerns make these issues critically important as we gain additional experience with this agent.

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